

Amendments to the Specification:

Please replace the paragraph at page 3, lines 8-22, with the following amended paragraph:

In another embodiment, this invention provides for antibodies that are cross-reactive with an anti-idiotypic antibody raised against F5 or C1. Thus, this invention provides for an antibody that specifically binds to a c-erbB2 receptor, where the antibody comprises at least 10 contiguous amino acids from the polypeptide sequence as set forth in SEQ ID NO: 1 or SEQ ID NO: 2, and where the antibody, when presented as an antigen, elicits the production of an anti-idiotypic antibody that specifically binds to a polypeptide sequence as set forth in SEQ ID NO: 1 or SEQ ID NO: 2; and the antibody does not bind to antisera raised against the polypeptide set forth in SEQ ID NO: 1 and SEQ ID NO: 2, that has been fully immunosorbed with the polypeptides set forth in SEQ ID NO: 1 and in SEQ ID NO: 2. These antibodies can share at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 1 or SEQ ID NO: 2 and have a binding affinity for c-erbB2 on cells of at least 10^{-5} M (10 μ M). The antibody may comprise an amino acid sequence that differs from the amino acid sequence of SEQ ID NO: 1 or SEQ ID NO: 2 by no more than 30 residues. The antibody may comprises a complementarity determining region (CDR) of SEQ ID NO: 1 or SEQ ID NO: 2.

Please replace the paragraph at page 4, lines 30-32, with the following amended paragraph:

This invention also provides for pharmaceutical compositions. The pharmaceutical compositions preferably comprise a pharmacological excipient and one or more of the F5-derived or C1-derived antibodies described herein.

Please replace the paragraph at page 4, lines 30-32, with the following amended paragraph:

Antibodies exist as intact immunoglobulins or as a number of well characterized fragments produced by digestion with various peptidases. Thus, for example, pepsin digests an antibody below the disulfide linkages in the hinge region to produce $F(ab')_2$, a dimer of Fab which itself is a light chain joined to V_H-C_H1 by a disulfide bond. The $F(ab')_2$ may be reduced under mild conditions to break the disulfide linkage in the hinge region thereby converting the $(Fab')_2$ dimer into an Fab' monomer. The Fab' monomer is essentially

an Fab with part of the hinge region (*see, Fundamental Immunology*, W.E. Paul, ed., Raven Press, N.Y. (1993), for a more detailed description of other antibody fragments). While various antibody fragments are defined in terms of the digestion of an intact antibody, one of skill will appreciate that such Fab' fragments may be synthesized *de novo* either chemically or by utilizing recombinant DNA methodology. Thus, the term antibody, as used herein also includes antibody fragments either produced by the modification of whole antibodies or synthesized *de novo* using recombinant DNA methodologies. Preferred antibodies include single chain antibodies (antibodies that exist as a single polypeptide chain), more preferably single chain Fv antibodies (scFv or scFv) in which a variable heavy and a variable light chain are joined together (directly or through a peptide linker) to form a continuous polypeptide. The single chain Fv antibody is a covalently linked V_H-V_L heterodimer which may be expressed from a nucleic acid including V_H- and V_L- encoding sequences either joined directly or joined by a peptide-encoding linker. Huston, *et al.* (1988) *Proc. Nat. Acad. Sci. USA*, 85:5879-5883. While the V_H and V_L are connected to each as a single polypeptide chain, the V_H and V_L domains associate non-covalently. The first functional antibody molecules to be expressed on the surface of filamentous phage were single-chain Fv's (scFv), however, alternative expression strategies have also been successful. For example Fab molecules can be displayed on phage if one of the chains (heavy or light) is fused to g3 capsid protein and the complementary chain exported to the periplasm as a soluble molecule. The two chains can be encoded on the same or on different replicons; the important point is that the two antibody chains in each Fab molecule assemble post-translationally and the dimer is incorporated into the phage particle via linkage of one of the chains to g3p (*see, e.g., U.S. Patent No: 5,733,743*). The scFv antibodies and a number of other structures converting the naturally aggregated, but chemically separated, light and heavy polypeptide chains from an antibody V region into a molecule that folds into a three dimensional structure substantially similar to the structure of an antigen-binding site are known to those of skill in the art (*see e.g., U.S. Patent Nos. 5,091,513; 5,132,405; and 4,956,778*). Particularly preferred antibodies include all those that have been displayed on phage I think preferred antibodies should include all that have been displayed on phage (*e.g., scFv, Fv, Fab and disulfide linked Fv*) (Reiter *et al.* (1995) *Protein Eng.* 8:1323-1331).

Please replace the paragraph at page 7, lines 5-7, with the following amended paragraph:

An "internalizing antibody" is an antibody that, upon binding to a receptor or other ligand on a cell surface is transported into the cell (*e.g.* into a vacuole or other organelle or into the cytoplasm of the cell).

Please replace the paragraph at page 7, lines 8-22, with the following amended paragraph:

As used herein, the terms "immunological binding" and "immunological binding properties" refer to the non-covalent interactions of the type which occur between an immunoglobulin molecule and an antigen for which the immunoglobulin is specific. The strength or affinity of immunological binding interactions can be expressed in terms of the dissociation constant (K_d) of the interaction, wherein a smaller ~~K_d~~ K_d represents a greater affinity. Immunological binding properties of selected polypeptides can be quantified using methods well known in the art. One such method entails measuring the rates of antigen-binding site/antigen complex formation and dissociation, wherein those rates depend on the concentrations of the complex partners, the affinity of the interaction, and on geometric parameters that equally influence the rate in both directions. Thus, both the "on rate constant" (k_{on}) and the "off rate constant" (k_{off}) can be determined by calculation of the concentrations and the actual rates of association and dissociation. The ratio of k_{off}/k_{on} enables cancellation of all parameters not related to affinity and is thus equal to the dissociation constant K_d (*see, generally, Davies et al. (1990) Ann. Rev. Biochem., 59: 439-473*).

Please replace the paragraph header at page 26, line 9, with the following amended header:

1) Generation of phage-display libraries.

Please replace the paragraph at page 30, lines 24-29, with the following amended paragraph:

An scFv can be expressed from this construct, purified by IMAC, and analyzed by gel filtration. To produce (scFv')₂ dimers, the cysteine is reduced by incubation with 1 mM β -mercaptoethanol, and half of the scFv blocked by the addition of DTNB. Blocked and unblocked scFvs are incubated together to form (scFv')₂ and the resulting

material can be analyzed by gel filtration. The affinity of the F5 and C1 scFv' monomers and the F5 and C1 (scFv')₂ dimers is determined by BIAcore.

Please replace the paragraph at page 37, lines 2-4, with the following amended paragraph:

In another embodiment, this invention provides for the epitope(s)₀ specifically recognized and bound by the F5 and C1 antibodies of this invention. This internalizing epitope is characterized by the ability to be specifically bound by F5 and C1 respectively. Thus, the F5 epitope is a region of c-erbB2 that specifically binds F5 (SEQ ID NO: 1) while the C1 epitope is a region of c-erbB2 that specifically binds C1 (SEQ ID NO: 1). It is believed that F5 and C1 both bind to the same c-erbB2 epitope.

Please replace the paragraph at page 69, lines 14-28, with the following amended paragraph:

Two unique phage antibodies were identified which were internalized by ~~SKRB3~~ SKBR-3 cells (F5 and C1 described above). Neither of these phage were isolated when the same library was selected on recombinant ErbB2. To determine why, the K_d of F5 (3.2×10^{-7} M) and C1 ($K_d = 1.0 \times 10^{-6}$ M) were measured. These K_d are significantly higher than the K_d measured for four of the scFv selected on recombinant ErbB2 ($K_d = 0.1$ to 0.65 nM). The higher K_d internalizing phage antibodies would have to compete with the lower K_d non-internalizing phage antibodies for selection on recombinant ErbB2 and were likely lost during the selection process. Since antibodies which are internalized as monomers are likely to be rare, and since there will be many more phage antibodies of lower affinity than higher affinity in a library, it is not surprising that the internalizing antibodies are of high K_d . Since antibodies which are internalized are likely to be rare, we hypothesized that it was likely that F5 and C1 recognized the same epitope. This was confirmed using a competition assay (Figure 2). Thus as hypothesized, F5 and C1 recognize the same epitope, and a different epitope than C6.5. Using the same assay, we confirmed that F5 and C1 recognize a different epitope than the Genentech anti-ErbB2 antibody 4D5 (when humanized known as Herceptin).